Prevalence of chronic kidney disease in the SardiNIA study cohort and its relationship to eGFR-related genetic loci and clinical risk factors.

Supplemental material

Figure S1: Distribution of SardiNIA Study cohort sample Compared to Distribution of Population by Age in the Territory of Ogliastra.

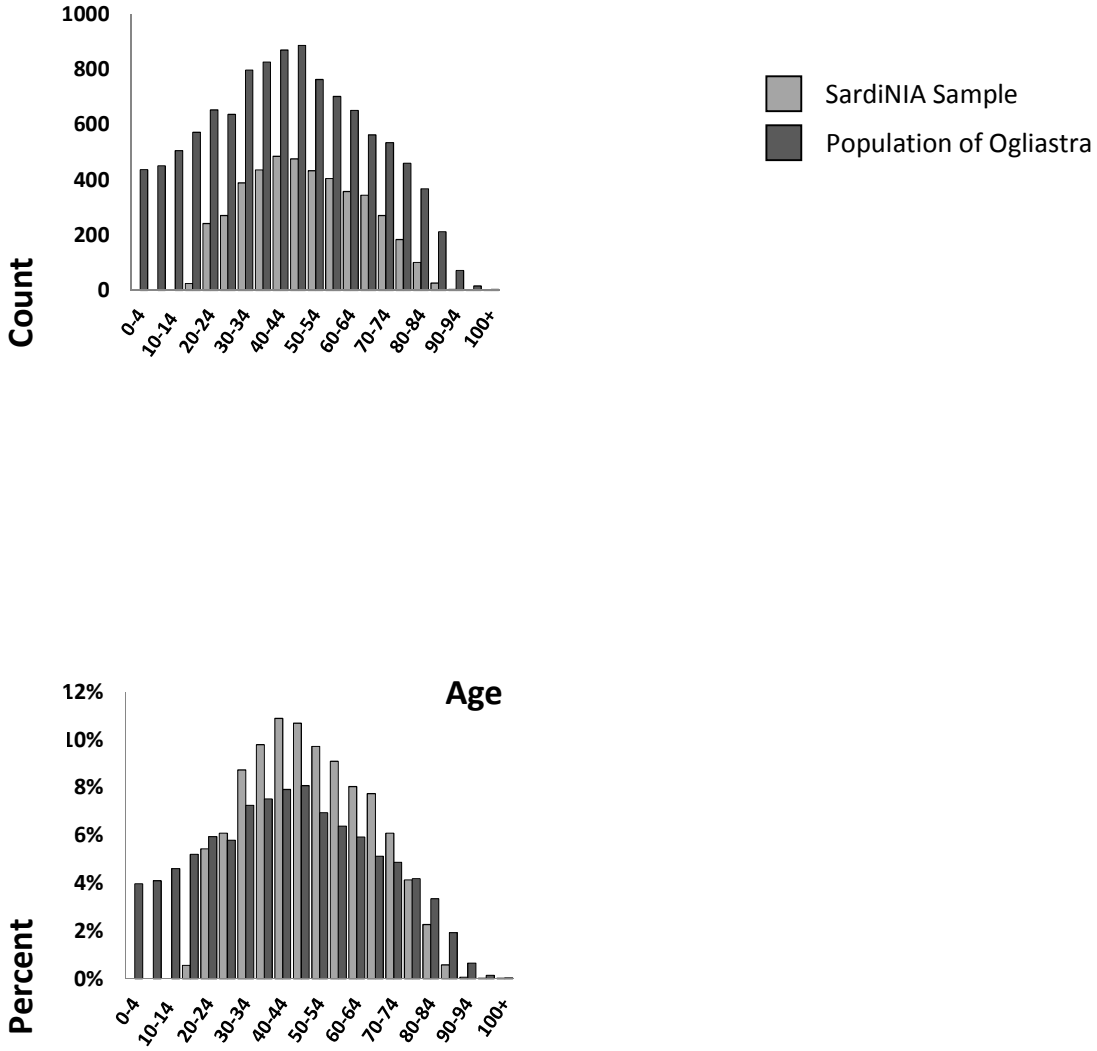
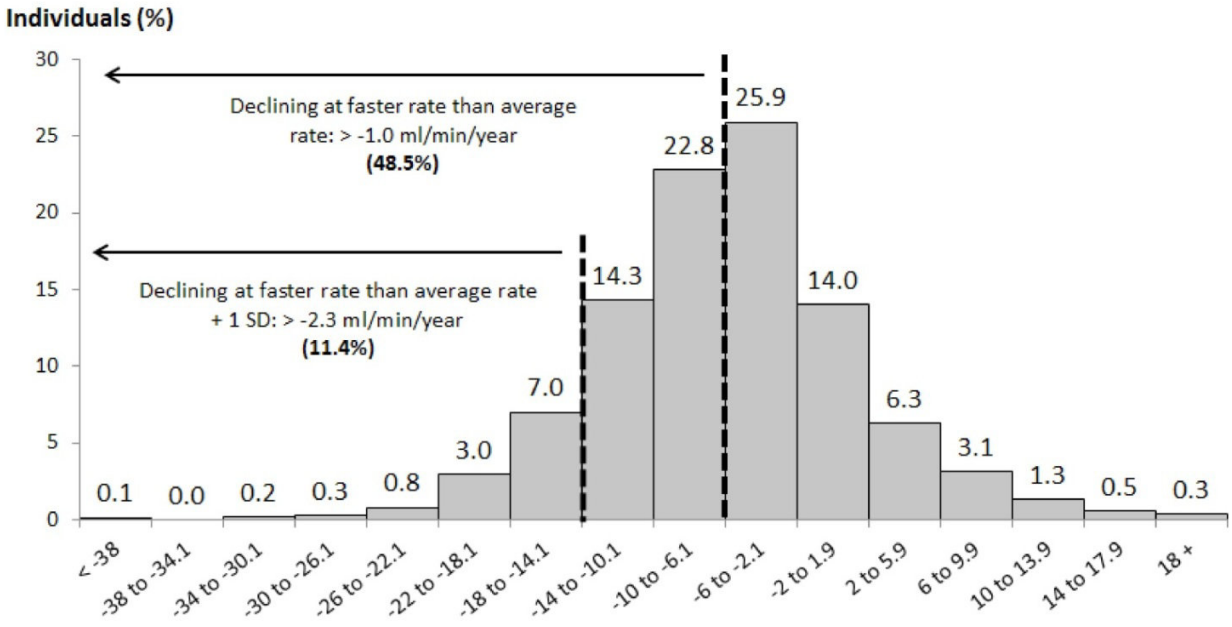
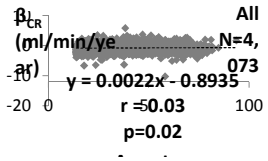


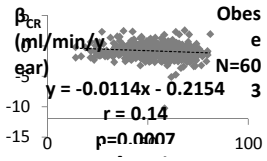
Figure S2. Histogram of change in eGFR over 7 years of study.

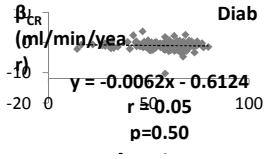


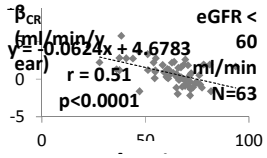
Individuals that declined faster than the average rate plus 1 SD were defined “fast decliners”.

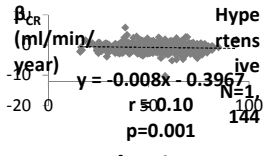
Figure S3. Regression coefficients plotting slope of eGFR vs. age at baseline (years) for: individuals who participated in all three visits











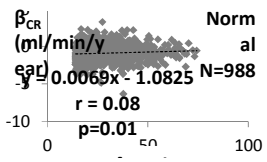
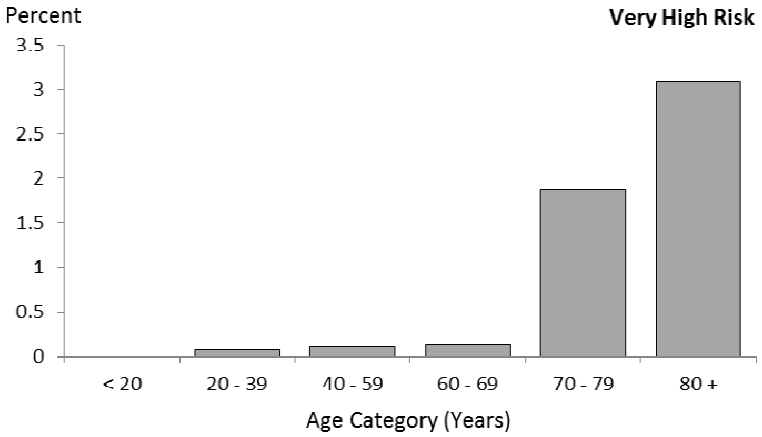
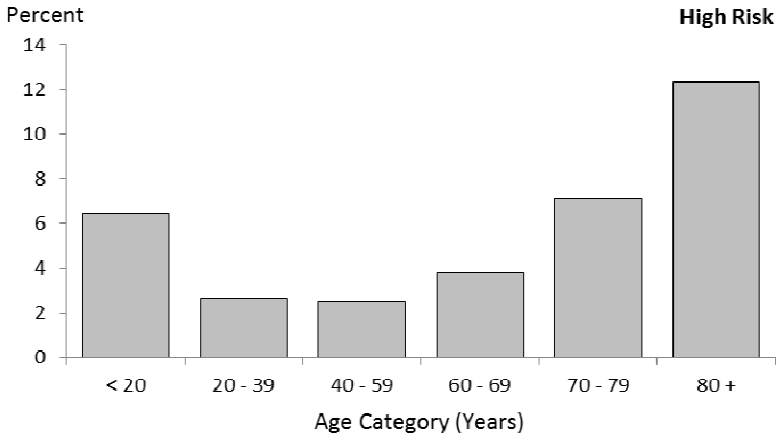


Figure S4. Prognosis of CKD according to KDIGO guidelines by age groups in SardiNIA study cohort individuals based on the third visit.





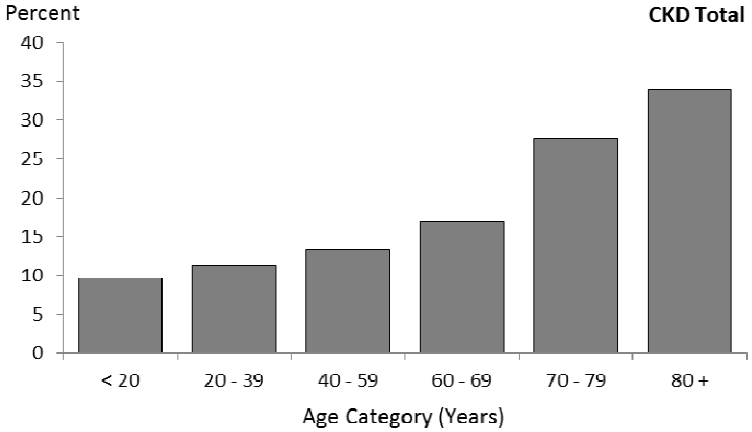


Figure S5. Prognosis of CKD according to KDIGO guidelines by risk factors in SardiNIA study cohort individuals based on third visit.

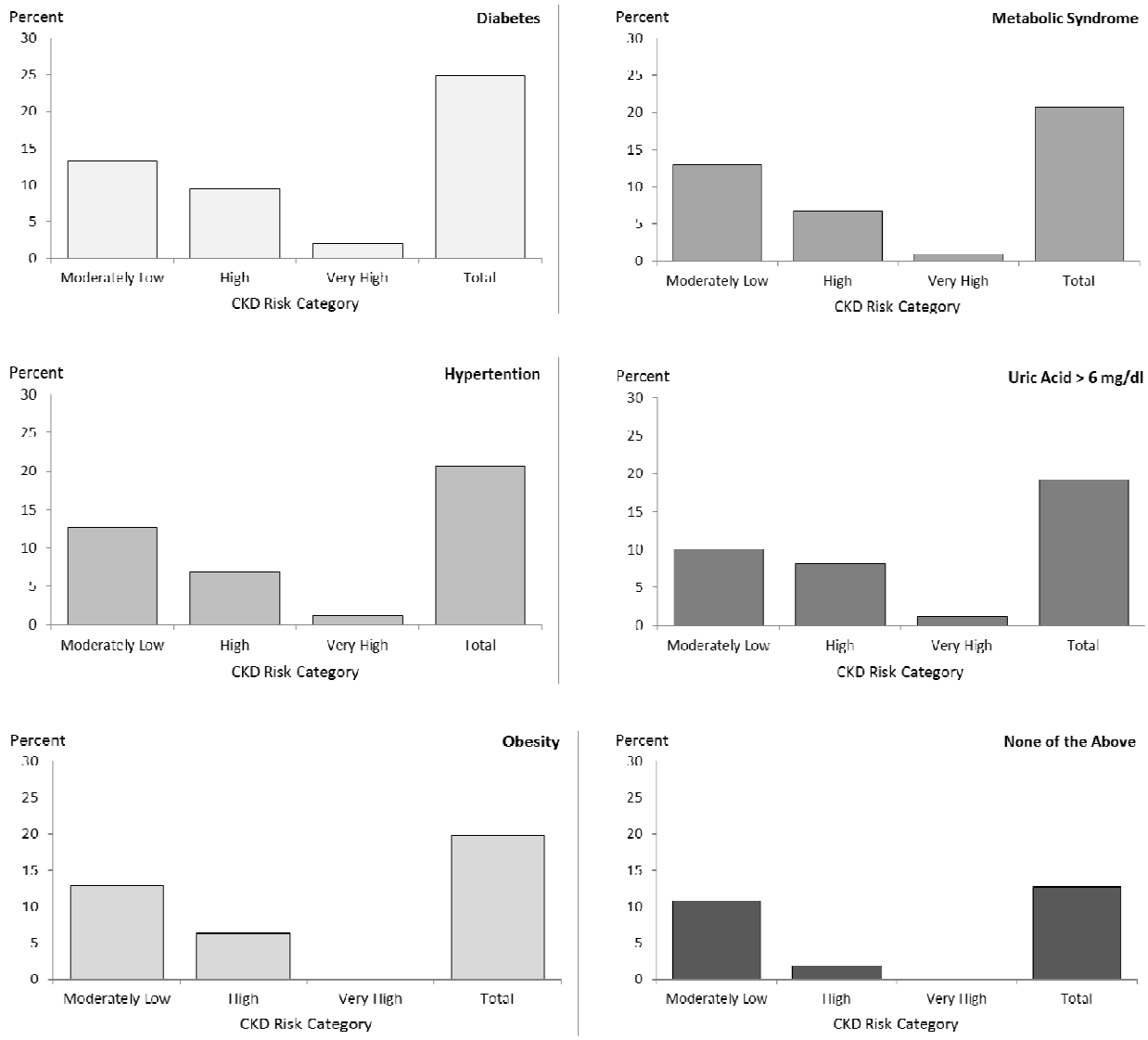


Figure S6. The graph shows the normal distribution of risk scores for the participants.

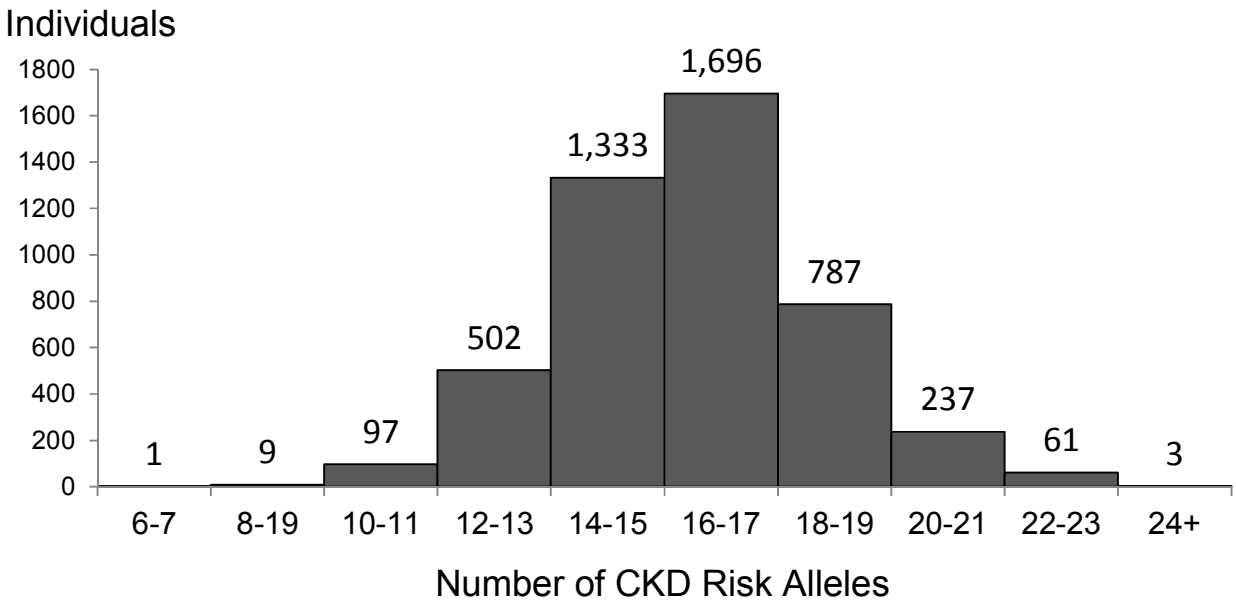


Table S1. Prevalence of CKD according to KDIGO guidelines in the third visit.

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012 N=4,471				Proteinuria categories, description and ranges (mg/dl)		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				< 30	30-300	>300
eGFR categories (ml/min/1.73 m2) Description and range	G1	Normal or high	≥90	2,674 (59.8%)	289 (6.5%)	80 (1.8%)
	G2	Mildly decreased	≥60 and < 90	1,108 (24.8%)	124 (2.8%)	57 (1.3%)
	G3a	Mildly to moderately decreased	≥45 and < 60	100 (2.2%)	5 (0.1%)	9 (0.2%)
	G3b	Moderately to severely decreased	≥ 30 and < 45	17 (0.4%)	1 (0.02%)	2 (0.04%)
	G4	Severely decreased	≥ 15 and < 30	1 (0.02%)	0 (0.0%)	2 (0.04%)
	G5	Kidney failure	< 15	1 (0.02%)	0 (0.0%)	1 (0.02%)

Complete material and methods

Screening and follow-up

Visits were repeated approximately every three years with 6,165 individuals completing a first visit; 5,256 completing a visit during the third to sixth year, and 4,842 completing a visit during the seventh to ninth years. Participants were interviewed during the first visit to collect socio-demographic information, medical and family history, lifestyle, health behaviors (smoking, drinking, coffee intake, etc.), and medications taken. Anthropometric measures (height, weight, and waist circumference) and resting blood pressure were determined. Blood samples were collected by venipuncture after an overnight fast of at least 12 h at each visit. Urine specimens were only collected at the third visit, in 92% of the participants. Blood tests included serum creatinine, uric acid, glucose, hemoglobin A1c (HbA1c), and lipid levels. At the third visit, urine dipstick proteinuria and microalbuminuria were determined (1).

Definitions

Diabetics were defined according to the guidelines of the American Diabetes Association as individuals with either HbA1c ≥ 6.5 %, or fasting plasma glucose (no caloric intake for at least 8 h) ≥ 126 mg/dl (7.0 mmol/L), or on anti-diabetic therapy, or when they reported a diagnosis of diabetes. Blood pressure (BP) was measured using a calibrated desktop sphygmomanometer after at least 5 minutes of supine rest. BP was measured three times at intervals of at least 5 minutes, and the reported BP was the average of the last two measurements. Volunteers were classified as hypertensive when BP was ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic, or when they reported taking antihypertensive medication. Obesity was defined as BMI (body mass

index) ≥ 30 kg/m2, according to the World Health Organization's definition. Abdominal circumference was considered high when it was >94 cm for men and >80 cm for women. Metabolic syndrome was defined according to the International Diabetes Federation (IDF) guidelines (2).

Cigarette smoking was defined as at least 10 cigarettes a day for a year. Previous cardiovascular (CV) events included coronary heart disease, heart attack, heart failure, or stroke, and were self-reported. Total cholesterol ≥ 200 mg/dl (5.18 mmol/L), triglycerides ≥ 130 mg/dl (1.47 mmol/L), LDL cholesterol (LDL-cholesterol)≥ 110 mg/dl (2.85 mmol/L), and uric acid serum levels ≥ 6 mg/dl (360 µmol/L) for women and ≥ 7 mg/dl (420 µmol/L) for men were considered high. HDL cholesterol (HDL-C) < 40 mg/dl (1.03 mmol/L) for men and < 50 mg/dl (1.29 mmol/L) for women was considered low.

As in Lindeman et al. (1985), we calculated the slope of eGFR for each individual and then created graphs with age at baselineon the x-axis and slope of eGFR on the y-axis for all individuals. Then we made comparable graphs for subgroups of individuals affected by diabetes, hypertension, obesity, with GFR< 60 ml/min/1.73m^2, and for those with no co-morbidities.

Design of multivariable models

We investigated the association between possible risk factors and 1) CKD (renal damage – defined as micro/macroalbuminuria and/or impairment of renal function); 2) change in eGFR; and 3) fast eGFR decline. We tested the following variables in the univariate analyses: age, gender, metabolic syndrome, obesity, abdominal obesity, diabetes, high glycaemia, hypertension, high blood pressure, previous cardiac disease, high uric acid, abnormal kidney length, smoking, major lipid profile, cortical thickness, and genetic score. The linear mixed models used to examine the association with change in eGFR also included baseline eGFR. All parameters that were significant ($p<0.05$) in univariate regression models were entered into a

full multivariable model. Final multivariable models included predictors that were significant at the $p<0.10$ level. In instances in which variables were known to be strongly correlated with one another (e.g., glucose and diabetes) only the one with the strongest association was included in the final model. We evaluated both the continuous and categorical variables, and since results were very similar, the categorical variables are shown for ease of interpretation.

Calibration of serum creatinine

Measurements of sCr in the SardiNIA Laboratory (NIALab) were performed with a kinetic alkaline picrate assay at the first and third visits, but using different instruments, a Bayer Express Plus Chemistry Analyzer at first visit and a Biosystem A25 Chemistry analyzer at third visit. Calibration was carried out by assaying 109 randomly chosen, thawed samples from the first visit at the Central Laboratory of the Brotzu Hospital (CLB), Cagliari, Italy, where sCr measurements were performed with an Olympus analyzer (Olympus Mishima Co., Ltd., Shizuoka, Japan), using Jaffe's kinetic method. The creatinine concentration for the serum calibrator was determined by the IDMS method.

A total of 63 randomly chosen specimens were also sent from the CLB to the NIA Lab for the measurement of sCr values, using the same instrument that had been used for the third visit analysis. Extreme outliers (difference > 3 standard deviations, SDs, from the mean) were excluded because they would not contribute useful information to the calibration. Deming linear regression (Y = CCRL on X = original serum creatinine) was conducted for each survey to correct the regression models for measurement error (3).

Two calibration equations were generated from the results and applied:

1) First/second visit: y (CLB) = -0.107+ 1.066*Creatinine NIALab

2) Third visit: y (CLB) = -0.195+ 1.0977*Creatinine NIALab

(Figure 1)

After standardization, we compared sCr values in subgroups of individuals in the same age range (40- 45 yr) and found that no statistically significant differences (Figure 2).

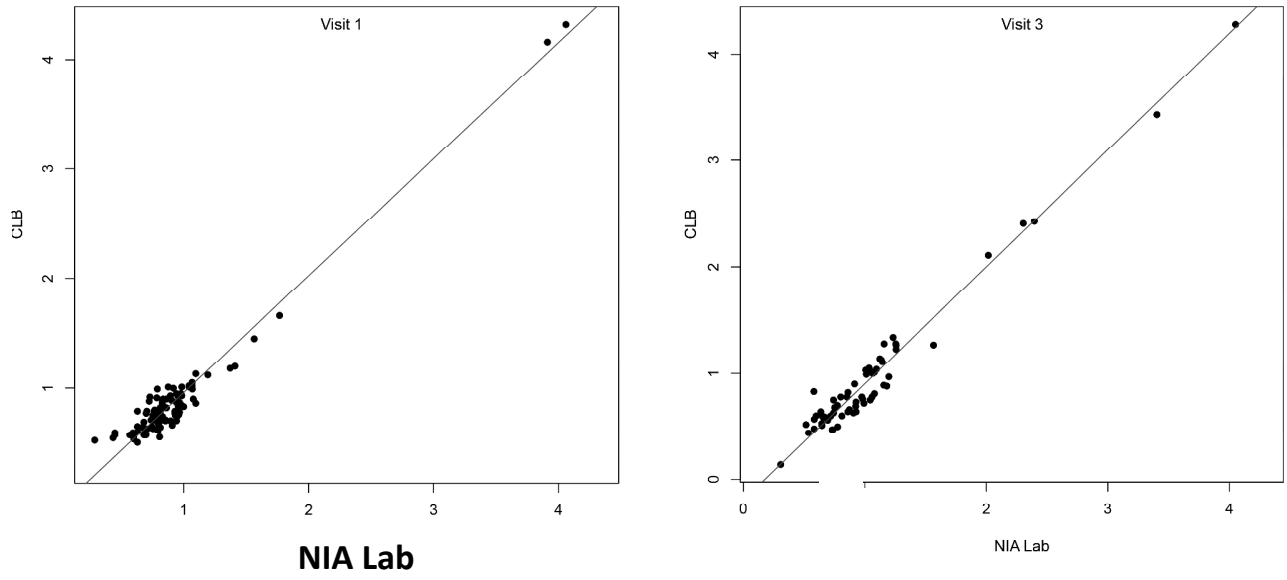
Online supplement references

1) Clark WF, Macnab JJ, Sontrop JM, Jain AK, Moist L, Salvadori M, Suri R and Garg AX,. Dipstick proteinuria as a screening strategy to identify rapidly renal decline. J Am Soc Nephrol 2011;22:1729-1736.

2) Alberti KG, Zimmet P, Shaw J. Metabolic syndrome--a new world-wide definition. A Consensus Statement from the International Diabetes Federation. Diabet Med. 2006 May;23(5):469-80).

3) Selvin E, Manzi J, Stevens LA, Van Lente F, Lacher DA, Levey AS, Coresh J. Calibration of serum creatinine in the National Health and Nutrition Examination Surveys (NHANES) 1988-1994, 1999-2004. Am J Kidney Dis. 2007 Dec;50(6):918-26.

Figure 1. Creatinine Calibration Plots for Visit 1 and Visit 3 in SardiNIA study cohort.



Deming linear regression was employed to correct the regression models for measurement error.

Figure 2. Comparison of sCr values in subgroups of individuals in the same age range (40- 45 yr) before (a) and after (b) standardization.